# Altered left ventricular contraction pattern during right ventricular pacing: assessment using real-time three-dimensional echocardiography

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Abstract: Background: Chronic right ventricular apical (RVA) pacing has been associated with increased risk of heart failure and adverse outcome. The acute effects of RVA pacing on three-dimensional (3D) ventricular function and mechanical dyssynchrony are not well known. We performed a real-time 3D echocardiographic (RT3DE) study to assess global and regional left ventricular function during RVA pacing. Methods: Twenty-six patients with implanted cardiac devices and normal intrinsic atrioventricular conduction were included in the study. RT3DE was performed during intrinsic sinus rhythm and during RVA pacing. Quantification of global and regional left ventricular function was performed offline by time-volume analysis of 16 myocardial segments. Time to reach minimum regional volume was calculated for each segment as a percentage of the cardiac cycle. The systolic dyssynchrony index (SDI) was defined as the standard deviation of these time periods. Longitudinal function was assessed by time-volume analysis of apical, midventricular, and basal segments. Results: During RVA pacing, a reversed apical-to-basal longitudinal contraction sequence was observed in 58% of all patients. RVA pacing was associated with increased left ventricular (LV) dyssynchrony (SDI increase from 4.4 ± 2.2% to 6.3 ± 2.4%, P = 0.001) and reduced LV ejection fraction (decrease from 53 ± 13% to 47 ± 14%, P = 0.05). Conclusion: RT3DE assessment of LV function provides evidence that pacing from the RVA results in acute alterations in LV contraction sequence and increased LV dyssynchrony. Further studies are warranted to assess the potential of RT3DE to identify patients who might be at increased risk of pacing-induced heart failure or who might benefit from alternate-site or multisite pacing. (PACE 2011; 76-81).

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*Original article*

# Altered Left Ventricular Contraction Pattern during Right Ventricular Pacing: Assessment using Real-Time Three-Dimensional Echocardiography

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## ABSTRACT

**Background:** Chronic right ventricular apical (RVA) pacing has been associated with increased risk of heart failure and adverse outcome. The acute effects of RVA pacing on three-dimensional ventricular function and mechanical dyssynchrony are not well-known. We performed a real-time three-dimensional echocardiographic (RT3DE) study to assess global and regional left ventricular function during RVA pacing.

**Methods:** 26 patients with implanted cardiac devices and normal intrinsic atrioventricular conduction were included in the study. RT3DE was performed during intrinsic sinus rhythm and during RVA pacing. Quantification of global and regional left ventricular function was performed offline by time-volume analysis of 16 myocardial segments. Time to reach minimum regional volume was calculated for each segment as a percentage of the cardiac cycle. The systolic dyssynchrony index (SDI) was defined as the standard deviation (SD) of these time periods. Longitudinal function was assessed by time-volume analysis of apical, mid-ventricular and basal segments.

**Results:** During RVA pacing, a reversed apical-to-basal longitudinal contraction sequence was observed in 58% of all patients. RVA pacing was associated with increased LV dyssynchrony (SDI increase from 4.4 ± 2.2 % to 6.3 ± 2.4 %, P=0.001) and reduced left ventricular ejection fraction (decrease from 53 ± 13 % to 47 ± 14 %, P=0.05).

**Conclusion:** RT3DE assessment of left ventricular function provides evidence that pacing from the RVA results in acute alterations in LV contraction sequence and increased LV dyssynchrony. Further studies are warranted to assess the potential of RT3DE to identify patients who might be at increased risk of pacing-induced heart failure or who might benefit from alternate-site or multisite pacing.

**Keywords:** Pacing; three-dimensional echocardiography; left ventricular function; dyssynchrony.

## Background

Chronic right ventricular apical (RVA) pacing has been associated with increased risk of heart failure and adverse outcome.[1] Nonphysiological ventricular activation induced by RVA pacing can result in abnormalities in left ventricular (LV) function. Altered LV contraction resulting in interventricular and intraventricular dyssynchrony may result in chronic LV remodelling[2] mitral regurgitation,[3] increased left atrial diameter[4] and reduced ejection fraction[5,6].

Echocardiographic analysis of RVA pacing reveals impaired global and regional wall motion abnormalities as assessed by wall motion score, electromechanical delay and regional strain.[7] However, few data exist on the acute effects of RVA pacing on three-dimensional ventricular function and mechanical dyssynchrony.[8] Real time three-dimensional echocardiography (RT3DE) allows functional assessment of global and segmental LV function.[9] The aim of this study was to characterize acute effects of RVA pacing by RT3DE assessment of global and segmental systolic function.

## Methods

### Patient characteristics

Consecutive patients with a cardiac pacemaker or an implantable cardioverter defibrillator (ICD) and preserved intrinsic atrioventricular (AV) conduction were enrolled in this study. All patients were scheduled for regular device follow-up in the institutional outpatient clinic and gave consent to RT3DE. Patients with regional wall motion abnormalities and pacemaker-dependent patients were excluded from this study.

**Real-time three-dimensional echocardiography**

RT3DE was performed by one experienced operator on a commercially available echocardiography system (ie33, Philips Medical Systems, N.A., Bothell, WA, USA) with an X4 matrix array transducer. Patients were imaged in the left lateral decubitus position. Apical full-volume datasets were acquired during one breathhold and were digitally stored for offline-quantification.

RT3DE data sets were acquired from each patient during sinus rhythm with intrinsic AV conduction, during asynchronous RVA pacing in patients with single-chamber devices, and during AV synchronous dual-chamber pacing in patients with dual-chamber devices. All devices were programmed to VVI mode with a minimal ventricular rate before acquisition of data sets during sinus rhythm with intrinsic conduction. Thereafter, devices were programmed to VVI mode (in single-chamber devices) or DDD mode (in dual-chamber devices) with a base rate slightly above the patient's sinus rate in order to achieve ventricular pacing. AV-intervals were adjusted using two-dimensional (2D) echocardiography and PW Doppler tracings of the mitral inflow to allow for physiologic diastolic filling. Twelve-lead electrocardiograms and telemetric marker channel recordings were used to ensure effective cardiac pacing and to rule out fusion beats.

Four-dimensional quantitative analysis of global and regional LV function was performed in a blinded fashion with a commercially available software package (Research Arena, version 2.0, TomTec Imaging Systems, Munich, Germany). Quantitative analysis involves defining several 2D slices through the voxelbased 3D data set as described previously.[9] In each slice, the endocardial border is traced with a semiautomated detection process, and a "cast" of the left ventricular cavity is created as a mathematical model to provide time-volume data for the entire cardiac cycle. By dividing this volume into pyramidal

subvolumes based around a nonfixed central point, it is possible to estimate time-volume data corresponding to each of the 16 standard myocardial segments, as defined by the American Society of Echocardiography. Systolic dyssynchrony indices (SDI) derived by RT3DE are obtained by calculating the time taken to reach minimum regional volume for each segment as a percentage of the cardiac cycle. The SDI is defined as the SD of these time periods. Higher SDI denotes increased intraventricular dyssynchrony.

To assess the longitudinal LV contraction sequence, LV function was analysed according to apical, midventricular and basal segments, respectively. Six basal subvolumes were combined for analysis of the basal segment, 6 midventricular subvolumes and 4 apical subvolumes for analysis of the midventricular and apical segments, respectively.

### Statistical Analysis

Continuous variables are expressed as mean ± SD. Nominal variables are expressed as numbers or percentages. Continuous variables were assessed with paired or independent-samples t-test and one-way ANOVA as appropriate. Nominal variables were compared by use of the chi-square test. A P value $\leq 0.05$ was considered statistically significant.

The study was conducted according to the regulations set forth by the regional ethics committee. All patients provided written and oral informed consent.

## Results

### Patient characteristics

The study population consisted of 26 patients (81% male, mean age 58 ± 16 years) without clinical evidence of congestive heart failure. Thirteen (50%) patients had been implanted with an ICD and 13 with a pacemaker. Eight patients with an ICD had coronary

artery disease, two had dilated cardiomyopathy, one had long-QT syndrome, one had isolated left ventricular non-compaction and one had idiopathic VT. Among pacemaker patients, two had been operated for aortic valve disease, one for mitral valve disease, and one had undergone coronary bypass surgery. Indication for pacemaker implantation was symptomatic AV block in 8 (62%) patients, sick sinus syndrome in two (15%), syncope in two patients, and symptomatic bradycardia in one (8%) patient. Indication for ICD implantation was survived cardiac arrest in 3 (23%) patients, documented symptomatic ventricular tachycardia in 8 (61%), and syncope in 2 (15%) patients.

At the time of device implantation, mean left ventricular ejection fraction, as assessed by 2D echocardiography, was 52 ± 14 among ICD patients and 63 ± 14 among pacemaker recipients. Since the date of device implantation, LVEF had decreased by 10% or more in three patients with a dual-chamber ICD, in two patients with a single-chamber ICD, and in one patient with a dual-chamber pacemaker. No patient had significant regional wall motion abnormalities during intrinsic rhythm. Single-chamber devices were used in 8 (31%) patients, and dual-chamber devices were used in 18 (69%) patients. The mean time after first implantation of a device was 6.0 ± 6 years. Four patients had undergone generator replacement due to battery depletion. In all patients devices had been programmed to allow for a minimum rate of RVA pacing. During the 12 months prior to enrolment in the study, the percentage of time that RVA pacing occurred was 10 ± 7%.

**Real-time three-dimensional echocardiography**

Full-volume RT3DE datasets could be successfully recorded and analyzed offline in all patients. Acquisition of echocardiographic data sets was completed within 19 ± 5 minutes. Offline analysis time was 27 ± 7 minutes. A total of 201 data sets were analyzed. Of those, 162 (81%) had sufficient quality for 4D quantitative analysis. No patient had to be excluded

because of insufficient image quality. Temporal resolution of the 3DE datasets was 19±14 volumes per second.

During sinus rhythm with intrinsic AV conduction, the mean LV ejection fraction (LVEF) was 53 ± 13%. During ventricular pacing, systolic ventricular function decreased (LVEF, 47 ± 14%, P = 0.05) and intraventricular mechanical dyssynchrony increased significantly (SDI, 6.3 ± 2.4% vs. 4.4 ± 2.2% during sinus rhythm, P = 0.001). The results of RT3DE measurements are presented in table 1. The decrease of LVEF (-8 ± 15% vs. -5 ± 15%, P = 0.64) and the increase of dyssynchrony (2.3 ± 1.3% vs. 1.8 ± 3.2%, P = 0.65) during RVA pacing did not differ significantly between patients with single chamber devices and those with dual-chamber devices. However, deterioration of left ventricular function was not observed in all patients. LVEF was reduced during ventricular pacing in 63% of patients with a single-chamber device, and in 67% of those with a dual-chamber device (P = 0.84). SDI increased during ventricular pacing in all patients with a single-chamber device, and in 72% of those with a dual-chamber device (P = 0.1). Figure 1 depicts the RT3DE contraction image sequence of a patient with a dual-chamber device during sinus rhythm with intrinsic AV conduction (left column) and during dual-chamber AV synchronous RVA pacing (right column).

The longitudinal systolic contraction was affected by RVA pacing. In 11 (42%) of all patients the sequence of ventricular contraction occurred simultaneously in the apical, midseptal and basal myocardial segments, or followed an apical-to-basal contraction sequence. In 6 patients with a single-chamber device (75%) and in 9 patients with a dual-chamber device (50%, p=0.1), this pattern was reversed, with the basal myocardial segments contracting prior to the ventricular apex. Time-volume curves demonstrating the longitudinal contraction sequence during RV pacing and during sinus rhythm with intrinsic conduction are shown in Figure 2.

## Discussion

Pacing from the RVA has been associated with a reduction in global systolic function and with alterations of regional contraction in patients with sick sinus syndrome.[8] Our present study extends these findings by demonstrating that RVA pacing not only induces left ventricular mechanical dyssynchrony in 70 percent of patients leading to an acute decline of LV ejection fraction in 60 percent of patients, but may also result in significant changes in the longitudinal systolic contraction sequence. Particularly, our data show that in more than half of the patients the longitudinal contraction pattern was reversed, with midventricular or basal contraction occurring prior to apical contraction. This reversal of the contraction pattern, which results in midsystolic "apical ballooning", can be observed in patients with both single- and dual-chamber devices. This finding may have important implications for selection of alternative pacing sites to minimize pacing-related LV dysfunction. The mechanism underlying this altered contraction pattern remains to be determined. Variations of electrode position at the RVA may play a role, as well as patient-specific factors influencing myocardial geometry and/or contractility.

Various attempts have been made to improve cardiac function by pacing from the high RV septum or RVOT.[10,11] Some studies have demonstrated a reduction in unfavorable cardiac remodeling[12] and a reduced incidence in myocardial perfusion defects[11] with RVOT pacing. However, epicardial alternate-site and multisite pacing did not improve cardiac output in patients undergoing cardiac surgery.[13] In a recent electrophysiological study, acute His bundle pacing did not improve LV function compared with alternate site pacing,[14] and no beneficial effect of outflow tract pacing could be observed in a long-term prospective crossover comparison.[10] Conversely, in patients with bradycardia and normal ventricular ejection fraction, biventricular pacing was able to prevent pacing-induced ventricular remodeling.[6]

Myocardial architecture and helical fibre orientation are important determinants of LV function during ventricular pacing. Optimal cardiac contraction is associated with a twisting movement with sequential timing and vigour of contraction. Organized action starts with shortening of the descending segment of the apical loop of the helical heart, then proceeds to the posterior segment and is finally followed by shortening of the ascending segment.[15] Univentricular stimulation initiates a premature impulse at the pacing site, and disrupts the orderly sequential progression of shortening along the helical heart spatial configuration.[15] Sonomicrometic studies in anaesthesized pigs have shown that LV dyssynchrony is due to disruption of the organized sequential movement of the successive components of the myocardial band, and results in loss of the normal clockwise twisting motion which is observed during efficient ejection.[16] Similarly, MRI tagging studies in dogs have demonstrated alterations in LV torsion during RVA pacing.[17] Our study provides RT3DE evidence of acute changes of the LV contraction sequence in humans, which suggests the presence of an altered pattern of LV torsion during RVA pacing.

*Clinical implications and study limitations:* The sample size of our study was adequate for detecting significant changes in LV function during RV pacing, but precluded detailed subgroup analysis. Inclusion of consecutive patients from a single center may have introduced selection bias and resulted in a rather inhomogeneous study group. Disease-related myocardial dysfunction and myocardial remodeling due to intermittent RV pacing may have influenced the study results. However, patients with regional left ventricular dysfunction were not included in the study. Each patient served as his or her own control, and no patient showed a reversed longitudinal contraction-pattern during intrinsic rhythm. Although RT3DE was feasible in all study patients, it may not be 100% feasible in other patient groups, especially in obese patients. 3DE datasets were obtained from gated acquisition of four partial volumes, and temporal resolution of RT3DE was limited to a maximum of 20 Hertz. In

general, the temporal resolution of 3DE is a trade-off with the spatial resolution. To increase spatial and temporal resolution, parallel processing is used as well as ECG gated acquisition of partial volumes. The amount of data that can be divided between the temporal and spatial resolution depends on the maximum feasible breath hold and the number of comparable cardiac cycles recorded during it.

The impact of acute changes in LV contraction sequence on long-term cardiac function and remodeling was not investigated. In a recent prospective study comparing RVA pacing with biventricular pacing, ejection fraction declined almost 7 percent points in the first year of RVA pacing in patients with normal ejection fraction. Ninety-eight percent of the patients in whom ejection fraction decreased to less than 45 percent at 12 months were in the RVA pacing group, suggesting that especially vulnerable patients might benefit most from biventricular pacing.[6] Further research is warranted to investigate whether RT3DE is useful to identify these vulnerable patients.

## Conclusion

This study provides RT3DE evidence that pacing from the RVA results in acute alterations in LV contraction sequence and in increased LV dyssynchrony. RT3DE is a valuable tool to assess acute pacing-induced changes in systolic LV function, including ejection fraction, SDI and longitudinal LV contraction sequence. Further studies are warranted to assess the potential of RT3DE to identify patients who are at increased risk of developing pacing-induced heart failure or who might benefit from alternate-site or multisite pacing.

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5

**Confict of Interest:** All authors state that they have no conflict of interest to declare.

**Figure 1.** RT3DE contraction image sequence of a patient with a dual-chamber device during sinus rhythm with intrinsic AV conduction (left column) and during dual-chamber AV synchronous RVA pacing (right column). The contraction front map (blue color indicates early contraction) demonstrates an apical-to-basal contraction sequence during sinus rhythm with intrinsic AV conduction, whereas during pacing, midventricular and basal contraction occurs prior to apical contraction.

**Figure 2.** Time-volume curves of a patient with a dual-chamber device during sinus rhythm with intrinsic AV conduction (Panel A) and during dual-chamber AV synchronous RVA pacing (Panel B). Relative volume changes of apical, midventricular and basal segments (Y-axis, percent) are depicted during one cardiac cycle (X-axis, percent). Note the altered longitudinal contraction sequence during RVA pacing, associated with prolongation of the ejection period.

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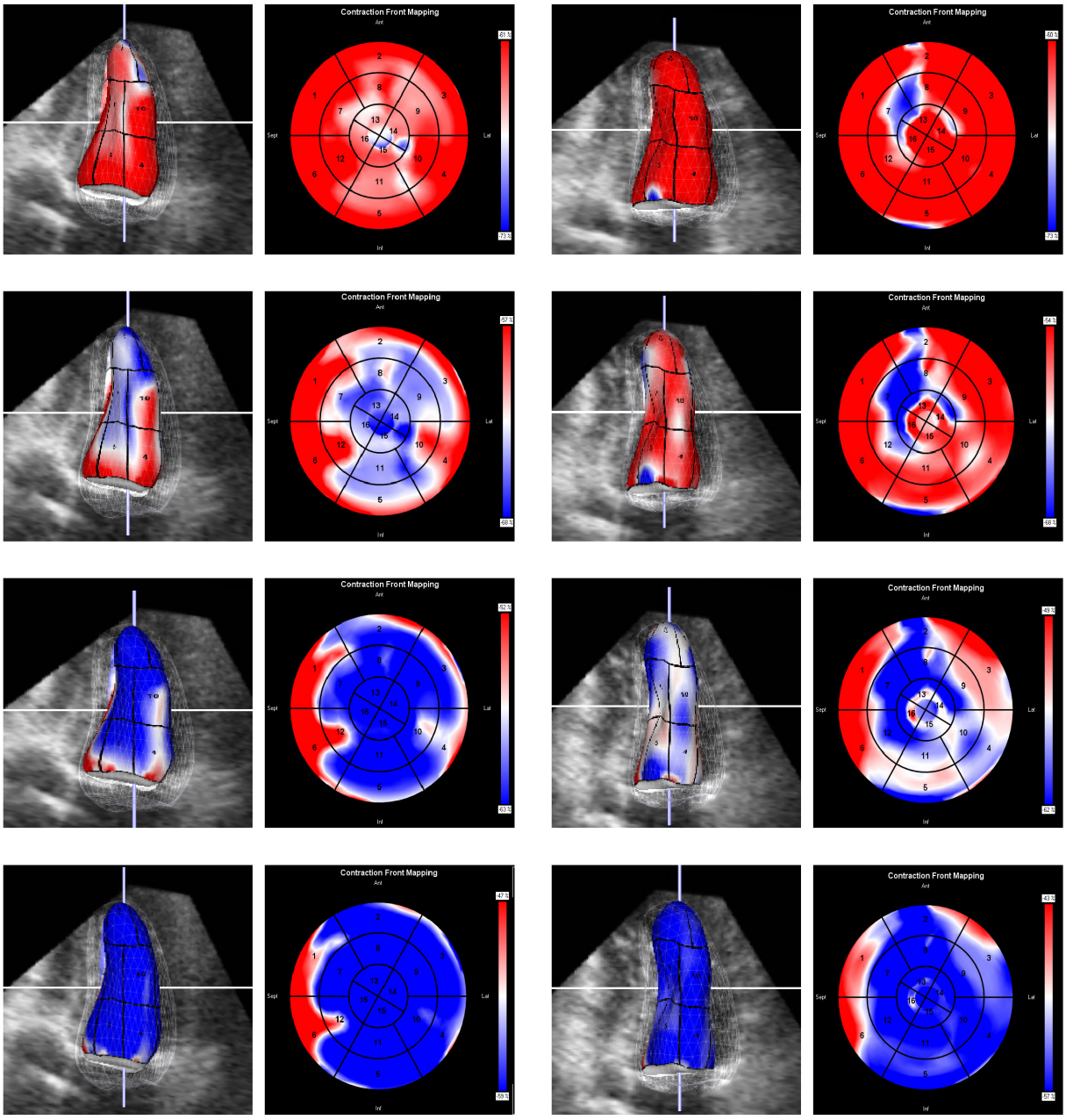
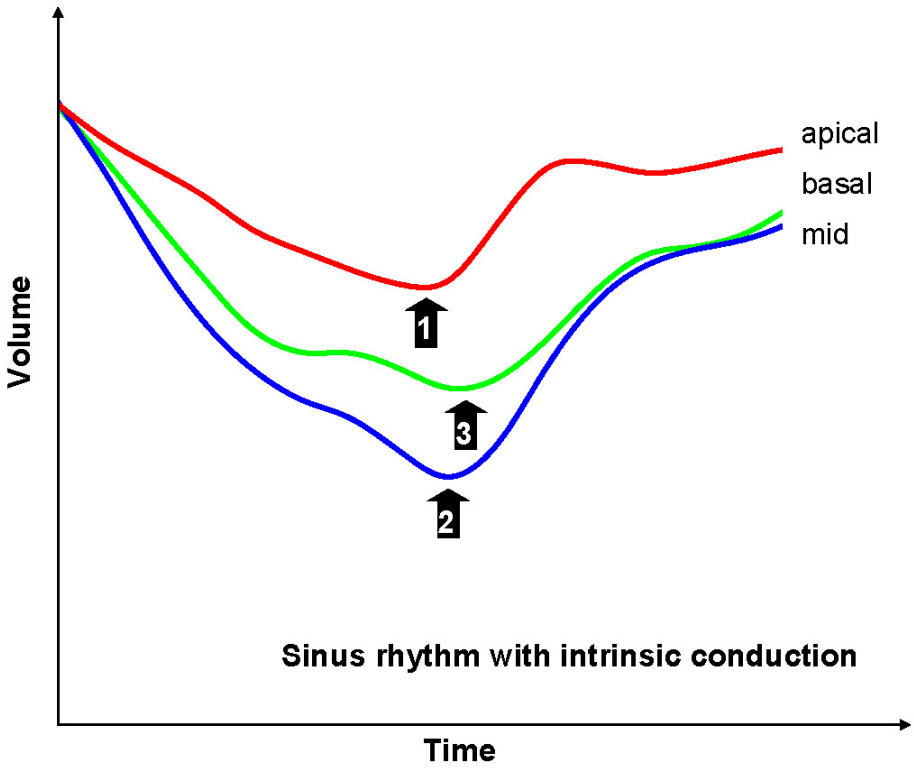
| | Single Chamber | | Dual Chamber | | Overall Group | |
|---|---|---|---|---|---|---|
| | n = 8 | P-value | n = 18 | P-value | n = 26 | P-value |
| LVESV | | | | | | |
| Sinus Rhythm | 41 ± 23 | 0.96 | 44 ± 27 | 0.30 | 43 ± 25 | 0.40 |
| Pacing | 41 ± 23 | | 41 ± 24 | | 41 ± 23 | |
| LVEDV | | | | | | |
| Sinus Rhythm | 77 ± 39 | 0.11 | 92 ± 38 | 0.07 | 87 ± 38 | 0.02 |
| Pacing | 67 ± 33 | | 79 ± 32 | | 76 ± 32 | |
| LVSV | | | | | | |
| Sinus Rhythm | 37 ± 20 | 0.05 | 48 ± 16 | 0.09 | 45 ± 18 | 0.02 |
| Pacing | 26 ± 14 | | 39 ± 17 | | 35 ± 17 | |
| LVEF | | | | | | |
| Sinus Rhythm | 48 ± 12 | 0.18 | 56 ± 13 | 0.19 | 53 ± 13 | 0.05 |
| Pacing | 40 ± 10 | | 51 ± 15 | | 47 ± 14 | |
| SDI | | | | | | |
| Sinus Rhythm | 4.0 ± 2.8 | 0.002 | 4.5 ± 2.8 | 0.03 | 4.4 ± 2.2 | 0.001 |
| Pacing | 6.3 ± 3.1 | | 6.3 ± 2.2 | | 6.3 ± 2.4 | |

**Table 1.** RT3DE findings of patients with single-chamber and dual-chamber devices during sinus rhythm with intrinsic AV conduction and during AV-synchronous RVA pacing.




Sinus rhythm

RVA pacing


apical
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Volume
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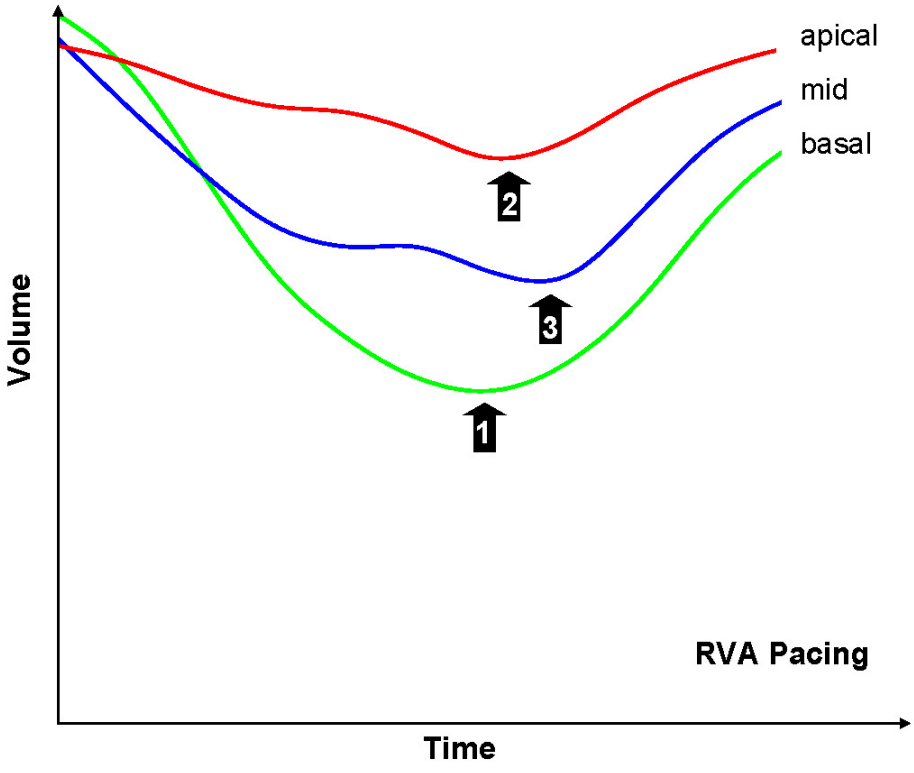
Sinus rhythm with intrinsic conduction
Time


apical
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